REMARKS

Applicants gratefully acknowledge the Examiner's decision to extend examination in the instant application to include second agents reading upon blocking molecules binding B7-1, B7-2, and CD28. Claims 1-14 were pending in the present application. Claims 5-6 and 8-14 have been withdrawn by the Examiner as being directed to non-elected inventions or species. Claims 1 and 3 have been amended herein. Claim 15 is new. Claims 2 and 4 have been canceled without prejudice. Upon submission of the instant response, claims 1, 3, and 5-15 are pending and claims 1, 3, 7 and 15 are under examination.

Support for the amendment to claim 1 may be found, for example, on page 3, lines 15-28 of the specification. Support for the amendment to claim 3 may be found, for example, on page 24, lines 22-33 of the specification.

Amendment or cancellation of claims should not be construed as an acquiescence, narrowing, or surrender of any subject matter. The amendments are being made not only to point out with particularity and to claim the present invention, but also to expedite prosecution of the present application. Applicants reserve the right to prosecute the originally filed claims further, or similar ones, in the instant or subsequently filed patent applications.

Specification

Applicants acknowledge the Examiner's general request to review the specification for errors in spelling, capitalization of TRADEMARKS, and the like.

Rejection of Claim 2 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 2 under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner contends that claim 2 is indefinite for the recitation of "or fragment thereof".

Applicants respectfully traverse the rejection. However, in the interest of expediting prosecution of the application, Applicants have canceled claim 2. Therefore, the rejection no longer applies.

Rejection of Claims 1-4 and 7[1] Under 35 U.S.C. § 112, First Paragraph: Written Description

The Examiner has rejected claims 1-4 and 7 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors were in possession of the claimed invention at the time of filing. Specifically, the Examiner objects to the use of the term "an agent which stimulates a CTLA4-associated apoptotic signal in the T cell", in claim 1. With respect to claims 3-4, related to the use of a second agent, the Examiner objects to the terms "second agent" and "blocking molecule".

Applicants respectfully traverse the rejection. However, in the interest of expediting prosecution, Applicants have amended claims 1 and 3 to more clearly define their scope. Applicants, therefore, respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 1-4 and 7 Under 35 U.S.C. § 112, First Paragraph: Enablement

The Examiner has rejected claims 1-4 and 7 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Specifically, the Examiner contends that undue experimentation would be required to practice the invention *in vivo*.

Applicants respectfully traverse the rejection. As the Examiner is aware, "[a]n in vitro…model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention" (M.P.E.P. 2164.02). Moreover, if "a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against

[1] The Examiner has referred to claims "1-32 and 48-50" in the Office Action. Since claims 1-4 and 7 are under examination, and claims 2-4 and 7 are dependent claims, Applicants have responded to the rejection as indicated.

correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications)" (M.P.E.P. 2164.02).

The *in vitro* T cell response assay utilized in the instant specification is a well-recognized and widely used model of *in vivo* T cell activation. Using this assay, Applicants have demonstrated that anti-CTLA4 antibody inhibits T cell proliferation and IL-2 production, and induces apoptosis in T cells. Given the exemplification set forth in the specification in a known and recognized model of T cell activation, a person of ordinary skill in the art could readily evaluate the activation or apoptotic response of T cells *in vivo*, and practice the claimed invention without undue experimentation.

The Examiner cites a number of references which allegedly support the position that *in vitro* assays do not correlate well with *in vivo* clinical trials in humans. None of these cited references teach unpredictability related to the use of the agents or combinations of agents recited in the instant claims. The Examiner cites several references disclosing antibody-mediated immunomodulation, without regard to whether the antibodies discussed in these references are agonistic or antagonistic. For example, the Examiner cites Daikh *et al.* (J Leukocyte Biol, 1997, 62: 156-162) as allegedly providing evidence for "exacerbation of diseases and the possible alteration of the development of autoimmunity with anti-CTLA4 antibodies (see pages 159-160)" (page 11, paragraph 3 of the Office Action). Page 160 of Daikh *et al.* states that "anti-CTLA4 mAb, which selectively blocks CTLA4-B7 interactions, exacerbates EAE" (emphasis added). In contrast, the instant claims recite agents which "stimulate a CTLA4-associated apoptotic signal" (emphasis added).

Moreover, the Examiner cites the clinical trial with TGN1412 (reviewed in Wadman, Nature, 2006, 440: 388-389 and Hopkin, Nature, 440: 855-856) as providing evidence for unpredictability in the art. TGN1412 is a super-agonistic anti-CD28 antibody, which activates T cells without the need for a second signal (Wadman). In contrast, the anti-CD28 antibodies cited in the instant claims are blocking antibodies, which inhibit signaling through CD28. The cited references provide no evidence that the clinical trial complications experienced with TGN1412 would indicate a likelihood of unpredictability in the use of the agents recited in the instant

claims. Moreover, according to Hopkin, "it might be no surprise that the compound, dubbed a 'superagonist' antibody by its creators, could run amok in the immune system." Thus, Hopkin indicates that the complications experienced in the TGN1412 clinical trial were not completely unpredictable. In light of all of the foregoing, Applicants submit that the practice of the claimed *in vivo* methods is enabled and would not require undue experimentation. Applicants, therefore, respectfully request reconsideration and withdrawal of the rejection.

Nonstatutory Obviousness-Type Double Patenting Rejections

The Examiner has provisionally rejected claims 1 and 2 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4, and 8-11 of U.S. Patent No. 6,719,972. Claim 2 has been canceled. Applicants respectfully request that the Examiner hold in abeyance all obviousness-type double patenting rejections based on said issued U.S. patent until allowable subjected matter is indicated, at which point Applicants will consider filing a terminal disclaimer.

CONCLUSION

Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at (617) 832-1000. If any fees are due, the Commissioner is hereby authorized to credit any overpayment or charge any deficiencies to **Deposit Account No. 06-1448, Reference No. WYS-020.02.**

Respectfully submitted,
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